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Pharmacokinetics and Penetration into the Aqueous Humor of Long Action Oxytetracycline after Single Dose Intravenous and Intramuscular Administrations in Rabbits

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Abstract: The aim of this study was to investigate pharmacokinetics and penetration into the aqueous humor of Long Action Oxytetracycline (OTC-LA) after Intravenous (IV) and Intramuscular (IM) administrations, at a single dose of 20 mg kg^{-1} b.wt in rabbits. After administrations of the long action formulation, the plasma oxytetracycline concentrations were evaluated using a two-compartmental open model. The study was designed according to a two-period cross-over and the plasma OTC concentration was measured using the ELISA procedure. The elimination half-lives ($t_{1/2\beta}$) of the OTC-LA after IV and IM administrations were 12.60±0.92 and 38.67±4.40 h, respectively. After IV administration, the volume of distribution (V_{dss}) and total body Clearance (Cl_{tot}) values of the drug were 3.42±0.21 L kg^{-1} and 0.19±0.01 L/h/kg, respectively. The maximum concentration of the drug (C_{max}) in the plasma (4.23±0.43 μg mL^{-1}) was achieved at 2.0 h (t_{max}) after IM administration. The Minimum therapeutic plasma Concentration (MIC) of the drug at the amount ≥0.5 μg mL^{-1} was maintained until 48 h after IV and IM administrations. The intramuscular bioavailability of the drug was 0.79±0.10%. After IV and IM administrations of OTC-LA formulation, the maximum concentrations of the drug in the aqueous humor were 0.1 and 0.068 μg mL^{-1}, respectively. However, the concentrations of the drug in the aqueous humor were below the MIC value (0.5 μg mL^{-1}) during 12-72 and 4-48 h for IM and IV administrations, respectively.

Key words: Oxytetracycline, rabbit, aqueous humor, pharmacokinetics, plasma, intravenous

INTRODUCTION

Oxytetracycline (OTC) is a broad-spectrum antibiotic that inhibits the growth of gram-positive and gram-negative bacteria including Rickettsia, Mycoplasma, Chlamydia and some protozoa. It is commonly used in veterinary medicine for the treatment of bacterial infections in respiratory and gastrointestinal tracts (Riviere and Spoo, 1995).

In order to reduce the cost of treatment and avoid repeated administrations, long action formulation of Oxytetracycline (OTC-LA) was prepared (Cornwell, 1980). The long action preparations of OTC have been used widely in various animal species (Riviere and Spoo, 2001).

Additionally, systemic administration of the OTC-LA formulation ensures an effective therapy for eye disease (keratoconjunctivitis) caused by *Moraxella bovis* in cattle, sheep and goats (Smith and George, 1985; George and Smith, 1985a; Ward and Clark, 1991). The pharmacokinetics of the OTC-LA formulation have been extensively studied in various animal species such as dogs (Kikuvi *et al*., 2001), sheep (Kaya *et al*., 2001), goats (Escudero *et al*., 1996), pigs (Gardner *et al*., 1989; Banting and Baggot, 1996) and cattle (Kumar and Malik, 1998).

The pharmacokinetics disposition of the OTC-LA in rabbits has not yet been documented, although McElroy *et al*. (1987) reported on the pharmacokinetics of conventional formulations of the OTC in rabbits.

The aim of the present study was to determine the pharmacokinetics of the OTC-LA and whether, it is possible to achieve therapeutic concentrations of long action oxytetracycline both in the plasma and the aqueous humor after a single dose (20 mg kg^{-1} b.wt), systemically administered in rabbits.

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MATERIALS AND METHODS

Reagents: The long action formulation of oxytetracycline (Engemycine 10% LA injectable formulation, 100 mg mL^{-1}, was used for the commercial preparation of OCT-LA) was provided by internet (Istanbul, Turkey). The local anesthetic, lidocaine (Atokain injectable formulation, 20 mg mL^{-1}, was used for the commercial preparation of lidocaine), was provided by Sanovel (Istanbul, Turkey). The ELISA kit (SuperScreen TETRA, code: AB 701) was purchased from Tecna (Trieste, Italy). The ELISA reader was from Bio-Tec (μQuat, KC-Junior program, Winooski, VT, USA).

Animals and experimental design: In this study, a total of twelve (n = 12) animals, which were approximately 9-12 months old were used. New Zealand white rabbits of both sexes were included. The rabbits had an average weight of 3.65±0.32 kg. Before testing, they were housed for 15 days in the Experimental Research Centrum at Ataturk University. These animals were fed pelleted feed (antibacterial-free) and water *ad libitum*. The animal experiments were performed in an ethically proper way by following guidelines set by the Ethical Committee of Ataturk University.

The present study was designed as a two-period cross-over. Four-week intervals were allowed between each period of the experiment. Before IV administration, the blood (2 mL) samples were collected from the right marginal vein of each animal for the control (at 0 min). The rabbits were divided into two groups (n = 6, for each group). Subsequently in group A, the OTC-LA was administrated into the semi-membraneous muscle in a single IM injection of 20 mg kg^{-1} b.wt. In group B, at the same dose, the OTC-LA was injected into the right marginal vein (using an IV injection). Blood samples were taken from the left marginal vein of each rabbit and collected in tubes containing the anticoagulant heparin. Samples were taken at 0.08, 0.25, 0.5, 1, 2, 4, 12, 24, 48, 72, 96 and 120 h after drug administration. The plasma was separated after centrifugation (3000 rpm min^{-1} for 5 min) within 1 h after collection. Plasma samples were stored frozen (at -20°C) until analysis. Additionally, aqueous samples (0.2 mL) were collected under local anesthesia (with lidocaine) at 4, 12, 24, 48, 72, 96 and 120 h after drug administration. All the samples were analysed within 1 week after the experiments. After a 4-weeks interval, administration was performed again.

Assay and sample preparation: The plasma and aqueous humor OTC concentrations were determined using the ELISA kit. Assay was performed according to ELISA procedure. For the preparation of the calibration curve, a standard solution (100 ng mL^{-1}) was diluted using standard diluent in the range of 0-100 ng mL^{-1}. Plasma samples were diluted with dilution buffer. The dilution factor is 100 (10 μL plasma sample +990 μL dilution buffer). However, the aqueous humor samples were not diluted. The calibration curve was prepared in the range of 0-100 ng mL^{-1}.

The sample preparation procedure was also achieved as described by ELISA prospectus. Briefly, the frozen plasma (0.5 mL) and aqueous humor samples (0.2 mL) were thawed at a temperature of 25°C (room temperature). The diluted plasma and aqueous humor samples were put in separate wells (50 μL). The receptor solution (50 μL) was added to the wells. The plate was shaken gently, using rotary motion, for a few seconds. It was then incubated for 30 min at room temperature. At the end of the incubation, the plate was washed three times using a washing buffer. Subsequently, 100 μL volume of enzyme conjugate was added to the wells. Again, it was shaken gently, using rotary motion, for a few seconds. The second time, it was incubated for 30 min at room temperature. The washing sequence was repeated as above. Developing solution (100 μL) was added to each well. The incubation was repeated as above. The stop solution (50 μL) was added to the wells. The absorbance was measured at 450 nm within a few minutes.

Pharmacokinetic and statistical analysis: The pharmacokinetic parameters were calculated by the two-compartmental analysis using a two-compartmental model WinNonlin 4.1 (WinNonlin® Professional Version 4.1, Pharsight Corporation, Scientific Consulting Inc., North Carolina, USA). The appropriate pharmacokinetic model was determined by application Akaike's information criterion (Yamaoka *et al*., 1978). The areas under the plasma concentration-time curves for both IV ($AUC_{IV0\to\infty}$) and IM ($AUC_{IM0\to\infty}$) studies were calculated using the method of trapezoids. The elimination half-life ($t_{½\beta} = 0.693/\beta$), the total body clearance (Cl_{tot} = Dose/AUC_{IV}) and the apparent steady-state volume of distribution (V_{dss} = ($Dose_{IV}$) (AUMC)/$AUC^2_{i.v}$) and bioavailability (F (%) = $AUC_{i.m}/AUC_{IV}$) were calculated. The peak plasma Concentrations (C_{max}) and time periods needed to reach peak concentrations (t_{max}) of the drug for the IM study were determined using the individual plasma concentration-time curves.

All results are presented as a mean±SD. Harmonic means were calculated for $t_{1/2ab}$, $t_{1/2\alpha}$, $t_{½\beta}$ and Mean Residence Time (MRT). SPSS 15.0 (SPSS for Windows, SPSS Inc., Chicago, II, USA) was used for calculated of the statistical differences in two groups between. The

Wilcoxon Signed Ranks test was used to test for significant differences between $t_{½\beta}$ and MRT. Comparisons of other pharmacokinetic parameters were made using the paired samples t-test. Statistical significance was assigned at $p<0.05$.

RESULTS AND DISCUSSION

In this study, the precision (RSD), the mean recovery and the limit of method detection were ≤7, 95% and 0.05 μg mL^{-1}, respectively. After IV and IM administration to rabbits at a single dose (20 mg kg^{-1} b.wt), the relationship between mean plasma and aqueous humor concentrations of the OTC-LA and lapsed time are shown in Fig. 1 and 2, respectively.

The mean plasma concentrations remained at >0.5 μg mL^{-1} until approximately 48 h after IV and IM administration, respectively. Also, the aqueous humor concentrations of the drug were maintained for 48 and 72 h for the IV and IM routes, respectively. After the IV and IM administrations of the OTC-LA formulation, the maximum concentrations of the drug in the aqueous humor were 0.1 (at 4 h) and 0.068 (at 24 h) μg mL^{-1}, respectively. However, the concentrations of the drug in the aqueous humor were below the MIC value (0.5 μg mL^{-1}) during 12-72 h and 4-48 h for IM and IV administrations, respectively.

The pharmacokinetics parameters (mean±SD) for the OTC-LA formulation, based on 2-compartmental analysis of the curves of each animal are shown in Table 1.

After administrations of the long action OTC formulation, the plasma oxytetracycline concentrations were evaluated using a two-compartmental open model. This is consistent with the results of previous studies on various animal species such as goats (Escudero *et al*., 1994; Payne *et al*., 2002), dogs (Kikuvi *et al*., 2001) and sheep (Kaya *et al*., 2001).

Until now, the pharmacokinetic disposition of the OTC-LA in rabbits has not been documented. However, McElroy *et al*. (1987) reported on the pharmacokinetics of a conventional formulation of OTC in rabbits. It should be noted that their study was only carried out using a conventional formulation and pharmacokinetics parameters were different from the results of the present study. Differences in product formulation may result in variations in pharmacokinetic parameters, even if the same animal species is used.

The Area Under Curve (AUC) is an important parameter, because it allowed us to determined the bioavailability (F%). In this study, after IM administration of the OTC-LA, the bioavailability was high (0.79±0.10%). This value was in agreement with the values for calves

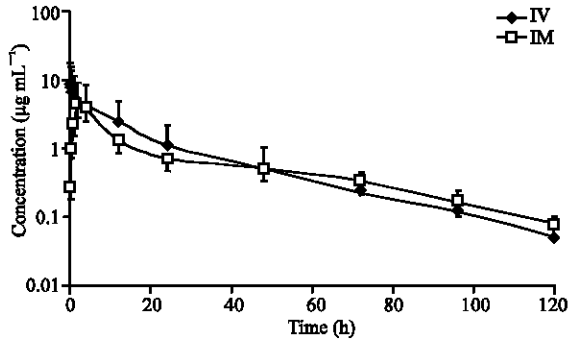

Fig. 1: Semilogarithmic plot of plasma concentrations time curves of oxytetracycline-LA after single dose IV and IM administrations at a dose of 20 mg kg^{-1} b.wt in rabbits (n = 6)

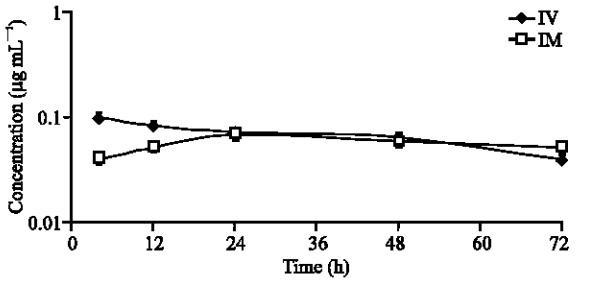

Fig. 2: Semilogarithmic plot of aqueous humor concentration time curves of oxytetracycline-LA after single dose IV and IM administrations at a dose of 20 mg kg^{-1} b.wt in rabbits (n = 6)

Table 1: Pharmacokinetic parameters determined after IV and IM administration of oxytetracycline-LA (20 mg kg^{-1}) (n = 6)

Parameters	Unit	IV	IM	p-value
K_{01}	h^{-1}	-	1.44±0.64	-
$t_{1/2ab}$ (HO)	h	-	0.48±0.78	-
α	h^{-1}	2.35±1.67*	0.30±0.04*	0.046
$t_{1/2\alpha}$ (HO)	h	0.40±0.22*	2.69±0.40*	0.043
β	h^{-1}	0.06±0.00*	0.02±0.00*	0.000
$t_{1/2\beta}$ (HO)	h	12.60±0.92*	38.67±4.40*	0.043
K_{12}	h^{-1}	0.87±0.59*	0.14±0.03*	0.045
K_{21}	h^{-1}	1.44±1.08*	0.06±0.01*	0.047
AUC	μg h mL^{-1}	104.31±5.24*	81.86±7.04*	0.011
Cl_{tot}	L h kg^{-1}	0.19±0.01	-	-
AUMC	-	1864±199	-	-
MRT (HO)	h	17.78±1.23	-	-
V_{dss}	L kg^{-1}	3.42±0.21	-	-
t_{max}	h	-	2	-
C_{max}	μg mL^{-1}	-	4.23±0.43	-
F	%	-	0.79±0.10	-

*Significantly different at $p<0.05$; α: Distribution rate constant; β: Elimination rate constant; $t_{1/2\alpha}$: Distribution half-life; $t_{1/2\beta}$: Elimination half-life; K_{01}: Absorption rate constant: $t_{1/2ab}$: Absorption half-life; K_{12} and K_{21}: First-order rate constants for drug distribution between the central and peripheral compartments; AUC: Area under the Curve from zero to infinity by the trapezoidal integral; V_{dss}: Apparent volume of distribution at steady-state; Cl_{tot}: Total body clearance; C_{max}: Maximum serum concentration; t_{max}: Time to peak concentration; F: bioavailability; HO; Harmonic mean

(89.1%, Kumar and Malik, 1998), sheep (73%, Kaya *et al*., 2001) and rabbits (71.4%, McElroy *et al*., 1987). In the present study, the maximum Concentration of the drug (C_{max}) in the plasma (4.23±0.43 μg mL^{-1}) was achieved 2.0 h after the IM administration. The obtained C_{max} value was somewhat similar to the values reported in dogs 4.39 μg mL^{-1} (Kikuvi *et al*., 2001), pigs 4.40 and 4.45 μg mL^{-1} (Archimbault *et al*., 1994), calves 5.7 μg mL^{-1} (Kumar and Malik, 1998) 5.2 μg mL^{-1} (Craigmill *et al*., 2000) and sheep 6.09 μg mL^{-1} (Craigmill *et al*., 2000) 5.13 μg mL^{-1} (Kaya *et al*., 2001). TerHune and Upson (1989) reported that after IM administration of a long action at double the label dose (40 mg kg^{-1} b.wt) in calves, the C_{max} of the drug was 9.6 μg mL^{-1}. In another study, two commercial OTC-LA formulations were administered to pigs at a dose of 30 mg kg^{-1} b.wt. The C_{max} values were determined to be 8.1 and 15.4 μg mL^{-1} (El-Korchi *et al*., 2001). In a previous study on camels, it was found that the C_{max} of the drug was 3.49 μg mL^{-1} after IM administration of a long action, at a dosage of 10 mg kg^{-1} b.wt (Oukessou *et al*., 1992). Comparisons of previous studies with the current study shows that there is a parallel dose between the C_{max} value of the drug. In the present study, the drug was used at a label dose (20 mg kg^{-1} b.wt) These differences in the C_{max} may be due to differences in animal species and dose level. The drug reached the peak plasma concentration at 2.0 h (t_{max}). Obtained results were consistent with previous results reported in pigs at 3.60 and 4.00 h (Archimbault *et al*., 1994), calves at 8 and 2.83 h (Kumar and Malik, 1998; Craigmill *et al*., 2000), sheep at 2 and 3.5 h (Kaya *et al*., 2001; Craigmill *et al*., 2000) and dogs at 0.72 h (Kikuvi *et al*., 2001). These differences in t_{max} may be related to both animal species and analysis methods (Koc *et al*., 2008). In this study, the concentrations of the drug were measured using the ELISA procedure. However, the concentrations were determined using High Performance Liquid Chromatography (HPLC) or bioassay methods in the above-mentioned studies. The results of the current study were consistent with reports by McElroy *et al*. (1987) in the same species: rabbits (4.7 μg mL^{-1}, at 2.09 h).

In the present study, the total body clearance (0.19±0.01 L/h/kg) of the OTC-LA was somewhat consistent in rabbits 0.434 L/h/kg (McElroy *et al*., 1987). However, this value was higher than the value reported in American alligators 0.007 L/h/kg (Helmick *et al*., 2004) and in calves 76.1 mL/h/kg (Kumar and Malik, 1998). This parameter may be directly affected by the extraction ratio and the organ blood flow in the different animal species (Rowland and Tozer, 1989). The differences in Cl_{tot} may be related to differences in animal species.

In this study, after IV and IM administrations were given, $t_{1/2\beta}$ values were achieved at 12.60±0.92 and 38.67±4.40 h, respectively. It is known that $t_{1/2\beta}$ is related to both V_{dss} and plasma clearance (Rowland and Tozer, 1989; Riviere, 1999). The observed $t_{1/2\beta}$ value in rabbits in the study was significantly longer than the value previously reported in the same animal species (McElroy *et al*., 1987). However, this value was somewhat similar to values reported in sheep (18.92 h), dogs (9.28 h), goats (14.4 and 29 h), calves (23.2 h) and pigs (68.512 and 69 h) (Kaya *et al*., 2001; Kikuvi *et al*., 2001; Payne *et al*., 2002; Escudero *et al*., 1994; Kumar and Malik, 1998; El-Korchi *et al*., 2001). In this study, the V_{dss} (3.42±0.21 L kg^{-1}) in rabbits was significantly larger than previously reported in many animal species, such as calves (0.86 and 3.30) (Kumar and Malik, 1998; Craigmill *et al*., 2000) and goats (1.44 L kg^{-1}) (Escudero *et al*., 1994). However, this value was not similar to the values reported in the same species (0.861 L kg^{-1}, McElroy *et al*., 1987). The larger V_{dss} indicates that the drug is widely distributed throughout the body tissues. It is known that the distribution pattern of a drug is related to the drug's ability to pass through tissue membranes (Rowland and Tozer, 1989). In the present study, the reason for differences between V_{dss} and $t_{1/2\beta}$ may be explained by the differences in the formulation of the OTC. In the above-reported studies, including the current study, long action formulations of the drug were used. In contrast, in the study reported by McElroy *et al*. (1987), a conventional formulation was used.

The previous studies have shown that the Minimum Inhibitory Concentrations (MICs) values of the OTC are approximately 0.5-1 μg mL^{-1} for various bacterial pathogens in different animal species (Kaya, 2002). In this study, the plasma concentration (>0.5 μg mL^{-1}) was maintained approximately 48 h for IV and IM administrations.

This concentration level was sufficient for the MICs needed for many bacteria isolates. After IV and IM administrations of the OTC-LA formulation, the maximum concentrations of the drug in the aqueous humor were 0.1 and 0.068 μg mL^{-1}, respectively. However, the concentrations of the drug in the aqueous humor were below the MIC value (0.5 μg mL^{-1}) during 12-72 h and 4-48 h for IM and IV administrations, respectively. George *et al*. (1985b) reported that the drug did not penetrate into the aqueous humor after IM injection (20 mg kg^{-1} b.wt) in calves. This result was inconsistent with previously reported studies. The results of this study indicate that the OTC-LA formulation provides the advantages of a longer dosage interval and therapeutic concentrations (0.5 μg mL^{-1}) that are maintained for a

long period in the plasma. However, the drug was not detected in the aqueous humor of rabbits in appreciable concentrations when administered to rabbits by IM and IV injections at a single dose of 20 mg kg^{-1} b.wt.

CONCLUSION

The OTC-LA formulation may be administered for treatment of bacterial diseases in 2 days intervals; however, systemic administration of the drug may not ensure an effective therapy in eye disease after IM injection in rabbits at a dose of 20 mg kg^{-1} b.wt.

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